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09/424,686	11/29/1999	GUSTAV HAGEN	BAYER10.203	8382

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EXAMINER
WALICKA, MALGORZATA A

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 04/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/424,686	HAGEN ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2003 and 31 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14,15,20-25,30-35 and 40-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14,15,20-25,30-35 and 40-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 November 1999* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *04/10/2000*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: reasons for allowable subject matter.

The Response to Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures filed on October 31, 2003, including the computer readable and paper forms of the sequence listing, as well as the statement regarding sameness thereof, is acknowledged. The Response has been entered.

The Response and Amendment under 37 CFR § 1.111 filed on July 27, 2003, is acknowledged. The amendments have been entered as requested. Claims 16-19, 26-29 and 36-39 are cancelled as drawn to the nonelected invention. Claims 14, 15, and 20-22 are amended. Claims 14-15, 20-25, 30-35 and 40-46 are pending in the Application.

As indicated in Summary of the Interview with biotechnology specialist C. Tsang, mailed to the Applicants on July 21, 2003, and reiterated in the letter of Oct. 6, 2003, Groups V to VIII, claims 14-15, 20-25, 30-35 and 40-46 are examined together in this Office Action.

DETAILED ACTION

1. Priority

Applicants priority to German applications 197 26 329.1 (June 20, 1997), 198 13 274.3 (March 26, 1998) and 198 16 496.3 (April 16, 1998) is acknowledged. The priority date granted for SEQ ID Nos; 1, 9, 10 and 12 is that of filing German Application 198 16 496.3, i.e. April 14, 1998, because only this application discloses SEQ ID Nos; 1, 9, 10 and 12. SEQ ID NO: 11 is disclosed only in the PCT Application

PCT/EP98/03468, which was filed on June 9, 1998 and for which one the instant application is the national stage.

2. Objections

2.1. Specification

The objection to the specification as containing a new matter in sequence listing made in the Office Action of April 22, 2003 is withdrawn, because the disclosure is complying with requirements for Patent Application Containing Nucleotide and/or Amino Acid Sequence.

The specification is objected to because of confusing statement of Applicants on page 9, line 30. Applicants state that their invention is related to the genomic sequence of human telomerase. Application does not disclose the genomic sequence.

Description of Fig. 2 is not corrected. Applicants write, "The DNA sequence depicted in Fig.1 can be completely translated from Position 64 to Position 3461 into an amino acid sequence." Actually, the open reading frame consists of nucleotides 63-3461. Translated nucleotides are 63-3458 and three nucleotides 3459-3461 are a stop codon.

The objection to the specification as containing numerous capitalizations of nouns and adjectives, for example, page 1 line 5, page 14, line 22, is not withdrawn, because the corrections have not been entered.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors in the specification of which applicant may become aware.

2.2. Claims

Claim 14 part e) is illegible in the first line.

2.3. Information Disclosure Statement

The IDS filed April 10, 2000 is written partially in English, partially in German. This IDS was signed by the examiner on August 6, 2001; copy enclosed. However, if Applicants wish to print the quoted documents on the patent, a substitute 1449 form filled out in English is required.

3. Rejections

3.1. 35 U.S.C. 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 34-35 and 40-43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as

to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are reciting the term "an antisense nucleic acid", however neither the claims nor the specification define the term "an antisense nucleic acid". It is unknown whether the antisense nucleic acid must be full-length complement or only a fragment.

The claims are also reciting the phrase "that binds to the nucleic acid sequence", however neither the claims nor the specification define the conditions of binding, thus rendering the claim indefinite. The claim should specifically recite the hybridization conditions used for binding the antisense nucleic acid sequence.

3.2. 35 USC, section 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3.2.1. Lack of written description

Claim 14, 15, 20-25, 30-35 and 40-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a variant nucleic acid sequence of SEQ ID NO: 1 SEQ ID NO:1 is further called DNA molecule encoding the reference telomerase, i.e. telomerase of SEQ ID NO: 2 that was described for the first time by Nakamura et al. Science, 277, 955-959, 1997, included in IDS. Claims are also directed to antisense nucleic acid binding said variant, to protein encoded by said variant, vector comprising said variant, host cells and recombinant production of the variant protein.

Claims 20-22, 30-32, 40-42 are rejected because of erroneous numbering of the nucleotides deleted in SEQ ID NO: 1 to obtain SEQ ID NOs: 9, 10 and 12. Applicants claim SEQ ID NO: 9 as the one derived from SEQ ID NO: 1 by deleting nucleotides 2184-2219; SEQ ID NO: 10 as the one in which nucleotides 2184-2219 and 2345-2526 have been deleted, and SEQ ID NO: 12 as derived from SEQ ID NO: 1 wherein nucleotides 3219-3842 have been replaced. The enclosed alignments of SEQ ID NOs: 9, 10 and 12 with SEQ ID NO: 1 indicate that this is not the case.

SEQ ID NO: 9 consists of SEQ ID NO: 1 wherein nucleotides 2183-2218 are deleted;

SEQ ID NO: 10 consists of SEQ ID NO: 1 wherein nucleotides 2183-2218 and 2345-2525 are deleted;

SEQ ID NO: 12 consists of SEQ ID NO: 1 wherein nucleotides 3221-3849 replaced.

As such, the proper description of structure of the claimed variants of SEQ ID NOs: 1 is lacking.

Claim 14, 15, 20-25, 30-33 and 44-45 are rejected because neither claim 14 parts a)-d) and dependent claims nor the specification recite the function of SEQ ID NOs: 9-12. Complete description of any compound should include description of both , its structure and its function (i.e. use). While the specification describes the complete structure of the polynucleotide of SEQ iD NO:9-12 it fails to describe the function/uses of the compounds. One skilled in the art realizes that a deletion in the encoding DNA molecule may render the encoded protein inactive, less active or change its enzymatic activity. The skilled artisan recognizes DNA molecules of SEQ ID NO: 9 and 10 as enzymatically inactive based on the teachings of the art. Deletion of nucleotides 2183-2218 which is an in frame deletion, results in lack of amino acids 708-719 which are located in motif A, or motif RT3 in Fig. 13 of the application, of the telomerase catalytic center. Killian et al. (Isolation of a candidate human telomerase catalytic subunit gene, which reveals complex splicing patterns in different cell types, Human Molecular Genetics, 1997, 12, 2011-2019, included in IDS) teach that a splice variant lacking motif A that is critical for reverse transcriptase is a dominant negative mutant. See page 2016, the right column, line 7, in the enclosed copy. In addition, Weinreich et al. Nature Genetics, 17, 498-502, 1997 have demonstrated that mutations in motif A inactivate telomerase; see Fig.3 in the article. Therefore one skilled in the art concudes that SEQ ID NO:9 and 10 are encoding dominant negative mutants of human telomerase.

The variant of SEQ ID NO: 12, having nucleotides 3221-3849 replaced seems to be a functional variant, because it misses C- terminal amino acids 1053-1132, which are not of critical importance to the catalytic activity of the reference telomerase.

The variant consisting of nucleotides 60-3470 of SEQ ID NO: 1 encodes the full-length human telomerase, consisting of 1133 amino acids, the first of which is alanine. From the second amino acid residue the protein is identical to SEQ ID NO: 2, because although the last codon, nucleotides 3468-3470, encodes proline, the open reading frame ends at the stop codon TGA, nucleotides 3459-3461. SEQ ID NO: 11, when expressed from an expression vector in a host cell gives the fully functional variant of the human telomerase.

Claim 14 part e) is directed to a nucleotide sequence that is at least 85% identical to the sequence described in part a), b) c) or d), or a sequence complementary thereof, wherein the encoded polypeptide has telomerase activity. Claim 14 part e) and claims 15, 24, 25, 34 and 44-are rejected for insufficient description of structure of the clamed invention.

Claim 14 part e) is directed to a genus of polynucleotides the structure of which is not sufficiently disclosed. No information, beyond the characterization of SEQ ID NO: 1, encoding SEQ ID NO: 2 has been provided by Applicants which would indicate that they had possession of the claimed genus of polynucleotides encoding the large genus of polypeptides having telomerase activity. Providing a single representative of the claimed genus is not sufficient for identifying the whole claimed genus of DNA molecules that are at least 85 % identical to SEQ ID NO: 9, 10, 11 and 12 and encode a

protein having telomerase activity, because Applicants do not which nucleotides of SEQ ID NO: 1 can be changed without the adverse effect on the function of the polypeptides. As the claimed genus is diverse in structure, the single species SEQ ID NO: 1 is not a representative of all members of the entire genus of polynucleotides that are within the scope of the claims, and is not sufficient to provide the identifying structural characteristics of the other members of the genus. The disclosure is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus.

In summary, the claimed polynucleotides are insufficiently described in the disclosure, and one skilled in the art cannot reasonably conclude that the Applicants had possession of the claimed invention at the time the instant application was filed.

2.2.2. Scope of enablement

Claim 14 part e) and claims 15, 24, 25, 34 and 44-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for polynucleotide of SEQ ID NO: 1 encoding reference human telomerase of SEQ ID NO: 2, and the variants thereof of SEQ ID NOs: 9-12 does not reasonably provide enablement for any DNA variant that is at least 85% identical to sequence of SEQ ID NO: 9, 10, 11 and 12 and exhibits human telomerase activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The claims are broader than the enablement provided by the disclosure with regard to

the large number of polynucleotides that are at least 85% identical to SEQ ID NOs: 9, 10, 11 and 12 and encoding active human telomerase. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Otherwise, undue experimentation is necessary to make the claimed invention. Factors to be considered in determining whether undue experimentation is required, are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the nature of the invention, (b) the breadth of the claim, (c) the state of the prior art, (d) the relative skill of those in the art, (e) the predictability of the art, (f) the presence or absence of working example, (g) the amount of direction or guidance presented, (h) the quantity of experimentation necessary.

The nature and breath of the claimed invention encompasses any polynucleotide that encodes activity of human telomerase, wherein said polynucleotide is at least 85 % identical to SEQ ID NOs: 9, 10, 11 and 12.

While methods of gene cloning and gene structure manipulations are well known in the relevant art, and skills of the artisans highly developed, one skilled in the art is not able to make any nucleotide sequence encoding human telomerase, which is at least 85% identical to SEQ ID NO: 9, 10, 11 or 12, or to obtain it from a natural sources, because the lack of sufficient structural characteristics of said variants makes the probability of success in obtaining the claimed invention low. The specification does not teach the function to structure relationship or which nucleotides of SEQ ID NO: 9, 10, 11, and 12 can be deleted, replaced or which and where should be added to obtain the DNA encoding for a protein of the desired activity; see the above rejection for lack of

written description. Thus, to make and use the claimed invention one skilled in the art is forced to do research outside the realm of routine experimentation. If a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should precede so that the claimed species have the functionality intended by Applicants. The provision of SEQ ID NO: 1 encoding SEQ ID NO: 2 fails to provide such guidance of the structure of any polypeptide which remain encompassed within the scope of the rejected claims.

Examiner concludes that without the further guidance on the part of Applicants in regards to structure of the claimed polypeptides, experimentation left to those in the art is improperly extensive and undue.

2.3. ***35 USC section 102***

The following is a quotations of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent, and

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 14 as well as 15, 24-25, 34-35 and 40-46 are rejected under 35 U.S.C. 102(e) as being anticipated by Cech et al. in the US Patent No. 6,093,836 (patent) issued on July 25, 2000, with priority to May 9, 1997.

Claims 14 part e), as well as 15, 24-25 and 44-46 are directed to polynucleotide sequence that is at least 85% identical to SEQ ID NO: 9, 10, 11 and 12, to proteins encoded by said sequences and having telomerase activity, antisense nucleic acid sequences, expressing vectors, host cells transformed with said vectors and the method of recombinantly producing polypeptides encoded by said polynucleotides.

The patent discloses SEQ ID NO: 224 encoding human telomerase of SEQ ID NO: 225, the reference human telomerase, that is identical to human telomerase of SEQ ID NO: 2 in the instant application; see copies of columns 57-60 of the patent.

SEQ ID NO: 224 of the patent is 100% identical to SEQ ID NO: 11 of the instant application. SEQ ID NO: 11 consists of nucleotides 53-3463 of SEQ ID NO: 224; see the enclosed sequence alignment.

SEQ ID NO: 224 of the patent is 98% identical to SEQ ID NO: 9 of the instant application; see the enclosed sequence alignment.

SEQ ID NO: 224 of the patent is 94% identical to SEQ ID NO: 10 of

the instant application; see the enclosed sequence alignment.

The patent teaches also expression of the nucleotide sequences encoding human telomerase, i.e. expression vectors and hosts, columns 22-26.

In conclusion, the patent anticipates claims 14 part e) as well as claims 15, 24, 25, 44, 45 and 46.

In addition, telomerase variant of SEQ ID NO: 11 is specifically rejected as claimed in claim 8 of the patent. The claim is directed to the DNA molecule comprising the encoding region of nucleotides 56-3451 of SEQ ID NO: 224. SEQ ID NO: 11 comprises nucleotides 56-3451 of SEQ ID NO: 224, because it consists of nucleotides 53-3463 of SEQ ID NO: 224; see the enclosed sequence alignment.

Claims 34-35 and 40-43 are also rejected under 35 U.S.C. 102(e)/(b) as being anticipated by the US Patent No. 6,093,809 (patent) issued to Cech et al. on July 25, 2000, with priority to May 9, 1997.

Claims 34-35 and 40-43 are generic and drawn to any antisense nucleic acid sequence that is antisense to:

1) SEQ ID NO: 9, i.e., SEQ ID NO: 1, wherein nucleotides 2184 to 2219 have been deleted;

2) SEQ ID NO: 10, i.e., SEQ ID NO: 1 wherein nucleotides 2183-2218 and 2345-2525 have been deleted;

3) SEQ ID NO: 12, consisting of SEQ ID NO: 1 wherein nucleotides 3221-3849 replaced;

4) SEQ ID NO: 11 consisting of SEQ ID NO: 1 wherein nucleotides 1-59 and 3471-4042 are deleted;

5) to any sequence that is at least 85% identical to the SEQ ID Nos: 9, 10, 11, and 12 or to the variants of these sequences that result from the degeneracy of the genetic code.

The patent teaches, column 34, line 45, subtitle "Therapeutic Use", methods of constructing and use of antisense molecules for human telomerase encoded by SEQ ID NO: 224. The scope of the genus of the antisense molecules for SEQ ID NO;224 comprises antisense molecules for DNA molecules enumerated under 1)-5) above. Also, SEQ ID NO: 224 itself or many of primers (see Table 3 in the copy of columns 57-58 of the patent) and fragments disclosed in the patent can be used as the nucleic acid molecule that is antisense to the variants disclosed in the instant application.

Thus the patent also anticipates claims 34-35 and 40-43.

4. Conclusion

No claim is in condition for allowance. The claims, however, contain allowable subject matter. The following is the examiner's reasons for allowable subject matter.

Applicants disclose nucleotide sequence of SEQ ID NO: 9, 10 and 12 encoding for human telomerase variants that are free of prior art and nonobvious. SEQ ID NO:9 and 10 can be use to produce the antisense inhibitor of telomerase expression, for

example in some cancer cells. Proteins encoded by SEQ ID NO:9 and 10 can be used as dominant negative mutants, i.e., for inhibiting the enzymatic activity of human telomerase, also in some cancer cells. One skilled in the art recognizes SEQ ID NO:12 as encoding catalytically active protein with potential application in therapy of disorders related to aging.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (571) 272-0944 and the right fax number is (571) 273-0944. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m. EST.

If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (571) 272-0928. The fax phone number for this Group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

Malgorzata A. Walicka, Ph.D.

Art Unit 1652

Patent Examiner

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PRIMARY EXAMINER
~~1800~~
1600